REMARKS

Claims 1-17 are pending in the application.

Claims 4 and 15 have been amended to remove dependency from non-elected subject matter, *i.e.* to remove dependency from claim 1. Claim 10 has been amended to correct a typographical error.

No new matter has been added. Applicant respectfully requests that the claim amendments be entered into the record of the instant application. For the Examiner's convenience, a copy of the claims that will be pending upon entry of the instant amendment is attached hereto as Appendix A.

Amendment of the claims should in no way be construed as an acquiescence to any of the rejections set forth in the instant Office Action, and was done solely to expedite the prosecution of the instant application. Applicants reserve the right to pursue the claims as originally filed in this or a separate application(s).

Requirement for Restriction and Election

The Office Action, on page 2, requires restriction to one of the following groups under 35 U.S.C. §121:

I. Claim 1, drawn to compounds classified in class 549, subclass 416+.

II. Claims 2-3, drawn to compounds classified in class 552, subclass 653.

III. Claim 17 drawn to packaged compound, classified in . . . class 424.

Applicant is required to elect one of the above groups for prosecution on the merits. During a telephone conversation with the Examiner on December 29, 1998, Applicant's attorney Elizabeth Hanley provisionally elected, with traverse, to prosecute the invention of Group II, claims 2-3. In addition, the Examiner indicated that claims 4-16 would be examined with the elected invention. Commensurate in scope therewith.

Applicant hereby affirms the election with traverse of the invention of Group II, encompassed by original claims 2-3. Claims 4 and 15 have been amended such that claims 4-16 are now commensurate in scope with the Applicant's election.

Applicant respectfully traverses the requirement for restriction of the subject matter of Groups I and III from the subject matter of Group II. Applicant believes that each of the above restrictions is improper on a number of grounds.

First, Applicant submits that the subject matter of the various groups represent different embodiments of a single inventive concept for which a single patent should issue. The pending claims represent an intricate web of knowledge, continuity of effort, and consequences of a single invention, which merit examination of all claims in a single application. Therefore, it is improper to require that the subject matter of these groups be prosecuted in separate patent applications.

Second, Applicant submits that a sufficient search and examination with respect to the subject matter of all claims can be made without serious burden. As the M.P.E.P. states:

> If the search and examination of an entire application can be made without serious burden, the examiner must examine it on the merits, even though it includes claims to independent or distinct inventions.

M.P.E.P. § 803 (7th ed., Rel. 78A, March 1999).

That is, even if the above-enumerated groups of claims are drawn to distinct inventions, the Examiner must still examine the entire application on the merits because doing so will not result in a serious burden. Applicant submits that the search and examination of Group II will have substantial overlap with the search and examination of Groups I and III, and no serious burden will result from searching and examining both groups in the same application.

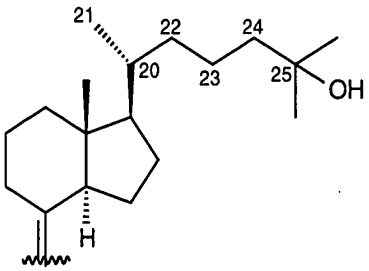
Accordingly, Applicant proposes that claims 1-17 be searched and examined in the instant application, and therefore respectfully requests reconsideration and withdrawal of the restriction requirement.

Claim Rejection under 35 U.S.C. § 102

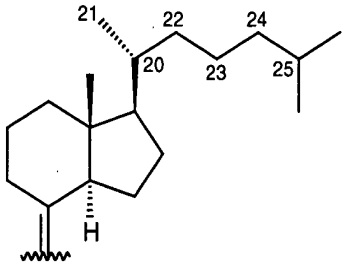
Claim 2 is rejected under 35 U.S.C. § 102(b) as being anticipated by Muralidharan *et al.*, *J. Org. Chem.*, 1993, **58(7):** 1895-1899. In particular, the Office Action, at page 3,

alleges that Muralidharan *et al.* disclose compound 4a on page 1896. Applicant respectfully traverses this rejection.

For ease of reference, the pertinent portions of compound 4a and claim 2 are reproduced below, with numbering of the carbon atoms:



Compound 4a



Claim 2 wherein:
$R_2=R_4=R_7=R_9=H$
$R_3=R_5=R_6=CH_3$
$A_1=A_2=A_3$=single bond

From the above comparison, it is clear that compound 4a has an hydroxyl group at the 25 position, while the structure recited in claim 2 does not. In other words, the compound in claim 2 has a hydrogen atom where compound 4a has an hydroxyl group. Moreover, whereas the specific compound of claim 2 depicted above has a methyl group in both the R_5 and R_6 positions, claim 2, as presently worded, does not include the possibility of either R_5 or R_6 being an hydroxyl group. Thus, compound 4a disclosed by Muralidharan *et al.* does not disclose every element of claim 2 and therefore cannot anticipate claim 2. Accordingly, Applicant respectfully requests reconsideration and withdrawal of the rejection of claim 2 under 35 U.S.C. § 102(b).

Claim Rejections under 35 U.S.C. § 103(a)

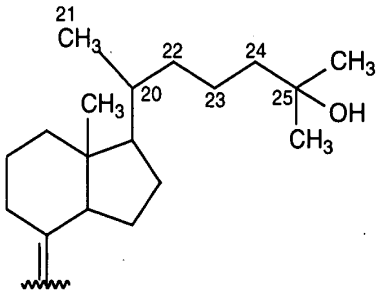
Rejection of Claim 2 under 35 U.S.C. § 103(a)

Claim 2 is rejected under 35 U.S.C. § 103(a) as being unpatentable over Fleet *et al.*, *Arch. Biochem. and Biophys.*, 1996 **329(2):** 228-234. The Office Action, at page 4, alleges that:

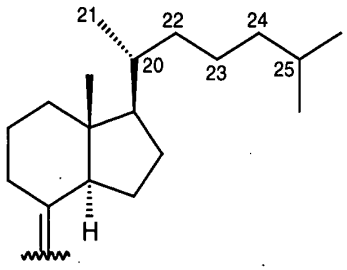
> Fleet et al., teach compound (1α, 3α), figure 1, page 229. The difference between the instant invention and that of Fleet et al., is that applicant's structure is an enantiomer instead of racemate structure by Fleet et al. Enantiomers and racemate are prima facie obvious absent a showing of unexpected results. In re Adamson, 125 USPQ 233. It would have been suggested to one of ordinary skill in the art to make the enantiomer. The motivation is to make additional compounds having antiproliferative effect.

Applicant respectfully traverses this rejection and submits that: (1) Applicant's claimed structure is ***not*** an enantiomer of the compound disclosed by Fleet *et al.*; (2) there is no motivation, teaching or suggestion, either in the cited reference or otherwise provided by the Office Action, for one of ordinary skill in art to modify the Fleet *et al.* reference to come up with Applicant's invention as claimed; and (3) even if there were such motivation, there is no expectation of success of making the claimed composition, either in the cited reference or elsewhere.

First, it is clear that the compound recited in claim 2 and the compound disclosed in Fleet *et al.* do not have the same chemical structure:



Fleet *et al.* Fig. 1



Claim 2 wherein:
$R_2=R_4=R_7=R_9=H$
$R_3=R_5=R_6=CH_3$
$A_1=A_2=A_3$=single bond

As is apparent from a comparison of the structures above, Applicant's claimed compound is ***not*** an enantiomer of the structure disclosed by Fleet *et al.* Rather, the two compounds have different chemical structures. That is, the compound in claim 2 has a hydrogen atom at the 25 position, whereas the Fleet *et al.* compound has an hydroxyl group. Moreover, while the specific compound of claim 2 depicted above has a methyl group in both the R_5 and R_6 positions, claim 2, as presently worded, does not include the possibility of either R_5 or R_6 being an hydroxyl group. Claim 2 recites a chemical structure that is different from the chemical structure of the Fleet *et al.* compound and, thus, no compound of claim 2 can be an enantiomer of the Fleet *et al.* compound. Therefore, the premise underlying the instant rejection of claim 2 under § 103 is false. Accordingly, the Office Action has not established a *prima facie* case of obviousness.

In addition, there is no teaching, suggestion or motivation for one of ordinary skill to modify the Fleet *et al.* compound to arrive at Applicant's claimed invention. No mention is made of Applicant's claimed structure, or how one would synthesize such compounds. Nor is there any indication that Applicant's claimed structure is even desirable. Moreover, at the time of the present invention, one of ordinary skill in the art would not have had a reasonable expectation of success in practicing the claimed invention. Nothing in the cited reference or Office Action suggests otherwise. Accordingly, the Office Action has failed to establish a *prima facie* case of obviousness for the invention as claimed.

In view of the foregoing, Applicant respectfully requests reconsideration and withdrawal of the rejection of claim 2 under 35 U.S.C. § 103(a).

Rejection of Claims 2 and 3 under 35 U.S.C. § 103(a)

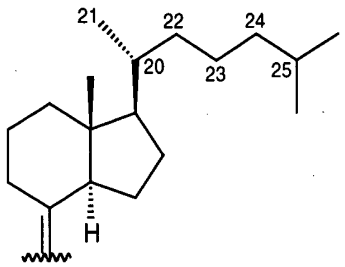
Claims 2 and 3 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Reddy *et al.*, *Biochemistry*, 1989, **28(4):**1763-1769. Specifically, the Office Action alleges:

> Reddy et al., teach compounds as shown on pages 1766 and 1768. The difference between the instant invention and that of Reddy et al., is that applicant's structure is an enantiomer instead of racemate structures by Reddy et al. Enantiomers and racemate are

prima facie obvious absent a showing of unexpected results. In re Adamson, 125 USPQ 233. It would have been suggested to one of ordinary skill in the art to make the enantiomer. The motivation is to make additional compounds having antiproliferative effect.

Applicant respectfully traverses the rejection and submits that: (1) Applicant's claimed structure is ***not*** an enantiomer of the compound disclosed by Reddy et al.; (2) there is no motivation, teaching or suggestion, either in the cited reference or otherwise provided by the Office Action, for one of ordinary skill in art to modify the Reddy *et al.* reference to come up with Applicant's invention as claimed; and (3) even if there were such motivation, there is no expectation of success of making the claimed composition, either in the cited reference or elsewhere.

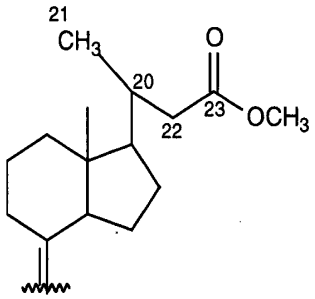
As discussed previously, Claim 2 is drawn to a compound with, among other things, the following structural portion:



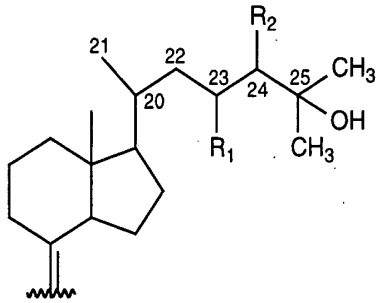
Claim 2 wherein:
$R_2=R_4=R_7=R_9=H$
$R_3=R_5=R_6=CH_3$
$A_1=A_2=A_3$=single bond

Furthermore, as the Office Action recognizes, claim 3 recites a species of generic claim 2.

In contrast, the Reddy *et al.* reference discloses compounds with the following pertinent, partial structures:



Reddy *et al.* p. 1766



Reddy *et al.* p. 1768

Once again, it is clear that the compounds claimed in pending claims 2 and 3 are ***not*** enantiomers of the compounds disclosed in the Reddy *et al.* reference. The Reddy *et al.* compounds do not have the same basic structure as the compounds of claims 2 or 3. For example, the compound depicted at page 1766 of Reddy *et al.* does not even have the same number of carbon atoms as recited in the relevant portion of claims 2 and 3. Moreover, the compounds disclosed on page 1768, are structures which have an hydroxyl group at position 25, similar to those previously discussed. Thus, the premise underlying the instant rejection of claims 2 and 3 under § 103 is false. Accordingly, the Office Action has not established a *prima facie* case of obviousness with respect to these claims.

In addition, there is no teaching, suggestion or motivation for one of ordinary skill to modify the Reddy *et al.* compound to arrive at Applicant's claimed invention. No mention is made of Applicant's claimed structure, or how one would synthesize such compounds. Nor is there any indication that Applicant's claimed structure is even desirable. Moreover, at the time of the present invention, one of ordinary skill in the art would not have had a reasonable expectation of success in practicing the claimed invention. Nothing in the cited reference or Office Action suggests otherwise. Accordingly, the Office Action has failed to establish a *prima facie* case of obviousness for the invention as claimed.

In view of the foregoing, Applicant respectfully requests reconsideration and withdrawal of the rejection of claims 2 and 3 under 35 U.S.C. § 103(a).

Objections

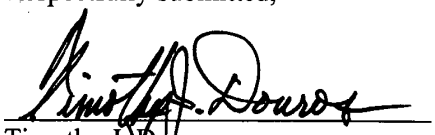
The Office Action, at page 4, objects to claims 4-16 because they contain non-elected subject matter. As explained above, claims 4 and 15 have been amended to remove dependency from non-elected claim 1. Thus, the objection to claims 4-16 has been obviated. Accordingly, Applicant respectfully requests reconsideration and withdrawal of the objection to claims 4-16.

CONCLUSION

In view of the foregoing remarks, Applicant respectfully requests reconsideration of the rejections and allowance of all pending claims.

If a telephone conversation with Applicant's attorney would expedite prosecution of the above-identified application, the Examiner is urged to call Applicant's attorney at (617) 227-7400.

Respectfully submitted,



Timothy J. Douros
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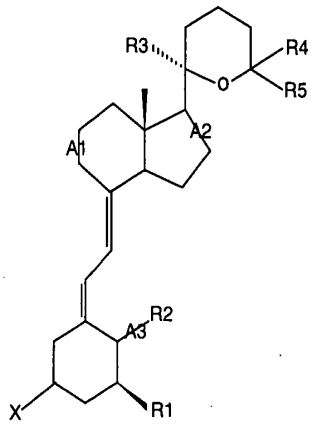
28 State Street
Boston, MA 02109
(617) 227-7400
Date: June 3, 1999

APPENDIX A

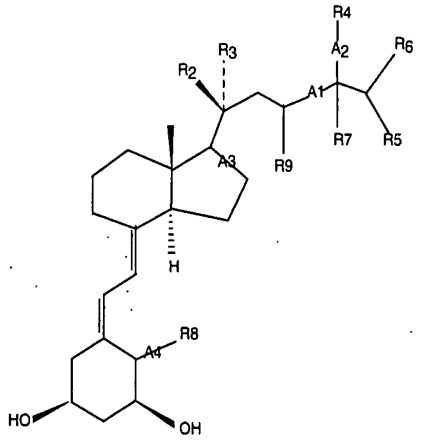
1. (Withdrawn) An isolated cyclic ether vitamin D3 compound having the formula (I) as follows:



I

, wherein A_1, A_2 and A_3 are a single or a double bond; X, R_1, R_2, R_3, R_4 and R_5 are selected from the group consisting of a hydrogen, a halogen, a haloalkyl, a hydroxy, a hydroxy-protecting group, an alkyl, an alkenyl, an alkynyl, an alkoxy, an aryl group and a heterocyclic group.

2. An isolated 3-epi form of 1α-hydroxy-vitamin D3 compounds having the formula II as follows:



II

, wherein A_1 is a single, a double, or a triple bond; A_2, A_3 and A4 are each independently selected from the group consisting of a single or a double bond; R_2, R_3, R_4, R_7, R_8 and R_9 are independently selected from the group consisting of a hydrogen, a deuterium, a

deuteroalkyl, a hydroxy, an alkyl, an alkoxide, an O-acyl, a halogen, a haloalkyl, a hydroxyalkyl, an amine or a thiol group, and wherein the pairs of R_2 and R_3, and R_4 and R_7 taken together are an oxygen atom; and R_5 and R_6 are independently selected from the group consisting of a hydrogen, a deuterium, a halogen, an alkyl, a hydroxyalkyl, a haloalkyl, and a deuteroalkyl.

3. The compound of claim 2, which is 1α(OH) vitamin D3, 1α,24 dihydroxy 3-epi vitamin D_3, 1α hydroxy 24-ethyl 3-epi vitamin D_3, 1α hydroxy 24-methyl 3-epi vitamin D_3, or 1α, 24-dihydroxy 24-methyl 3-epi vitamin D_3.

4. A method of treating a disorder characterized by an aberrant activity of a vitamin D_3-responsive cell, comprising administering to a subject an effective amount of a vitamin D_3 compound of claim 2, such that the aberrant activity of the vitamin D_3-responsive cell is reduced.

5. The method of claim 4, wherein the disorder comprises an aberrant activity of a hyperproliferative skin cell.

6. The method of claim 4, wherein the disorder comprises an aberrant activity of an endocrine cell.

7. The method of claim 6, wherein the endocrine cell is a parathyroid cell and the aberrant activity is processing and/or secretion of parathyroid hormone.

8. The method of claim 7, wherein the disorder is secondary hyperparathyroidism.

9. The method of claim 8, wherein the disorder comprises an aberrant activity of a bone cell.

10. The method of claim 9, wherein the disorder is selected from the group consisting of osteoporosis, osteodystrophy, senile osteoporosis, osteomalacia, rickets, osteitis fibrosa cystica, renal osteodystrophy, secondary hyperparathyrodism, cirrhosis, and chronic renal disease.

11. The method of claim 4, wherein the subject is a mammal.

12. The method of claim 11, wherein the mammal is a human.

13. A method of ameliorating a deregulation of calcium and phosphate metabolism, comprising administering to a subject a therapeutically effective amount of a 3-epi vitamin D_3 compound of any of claims 2 or 3, so as to ameliorate the deregulation of the calcium and phosphate metabolism.

14. The method of claim 13, wherein the deregulation of the calcium and phosphate metabolism leads to osteoporosis.

15. A pharmaceutical composition comprising, a therapeutically effective amount of a vitamin D_3 compound of claim 2, and a pharmaceutically acceptable carrier.

16. The composition of claim 15, which is suitable for topical or oral administration.

17. (Withdrawn) A packaged compound, comprising a vitamin D_3 compound of any of claims 1 or 2, packaged with instructions for use of the compound for treating a disorder characterized by an aberrant activity of a vitamin D_3-responsive cell.